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Bullous pemphigoid and dipeptidyl peptidase 4 inhibitors: a prospective case-control study in an Italian population

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The knowledge regarding the risk of bullous pemphigoid (BP) in patients with type 2 diabetes (T2D) taking dipeptidyl peptidase 4 inhibitors (DPP4i) is based on case reports, pharmacovigilance database analyses, randomized clinical trials and retrospective observational studies. To further investigate the relationship between taking DPP4i and the risk of BP and to characterize demographic, clinical and immunological profile of DPP4i associated patients we conducted a prospective case-control study in an Italian population. Two hundred and nine BP and 308 T2D consecutive patients were enrolled in two referral centers for autoimmune bullous diseases from 2019 to 2022. One hundred and eight patients were BP, while one hundred and one were T2D BP (48%), demonstrating a high prevalence of T2D in BP patients. Almost half of T2D BP patients were DPP4i users showing that 1 of 4 BP patients had an induced disease caused by a known drug. Overall, DPP4i intake was associated with a 2.3-fold increased risk for BP (95% CI, 1.7-3.0) and the most used DPP4i was linagliptin with a 2.1-fold increased risk for BP (95% CI, 1.2-3.7). It is interesting to note that mean age increased together with the male proportion from 108 non-T2D BP to 51 non-DPP4i users T2D PB and to 50 DPP4i users T2D PB (75.0 years old and male 50%; 77.9 years old and male 51%; 80.0 years old and male 60%, respectively). Immunoglobulin (Ig)G humoral response of DPP4i users BP to BP180 and BP230 antigens was reduced in frequency and titers compared with those of patients non-DPP4i users. In particular, a peculiar immunological profile was characterized by reactivity to multiple BP180 epitopes. This study demonstrates that treatment with DPP4i, especially linagliptin, was significantly associated with an increased risk of BP among T2D patients. In addition, DPP4i users BP present specific demographic and immunological features.

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Sebaceous glands are actively and differentially involved in the pathogenesis of atopic dermatitis and psoriasis as revealed by spatial transcriptomics

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The primary function of sebaceous glands (SGs) is to produce the lipid rich sebum and thereby contribute to hair and skin lubrication. Recent findings however revealed that SGs may have immunoregulatory functions as well. We performed spatial transcriptomics (ST) on lesional and autologous non-lesional human skin samples of patients with psoriasis (PsO), atopic dermatitis (AD). Differentially expressed genes were identified followed by pathway enrichment analysis. Finally, a meta-analysis was done using RNAseq data from SZ95 human sebocytes treated with a combination of IL17 and TNFa to mimic the effect of a PsO-like microenvironment. Besides confirming that SGs contribute to skin homeostasis with a cell type specific lipid metabolism, we identified a large set of genes that were so far not known to be expressed in in-vivo SGs. In PsO samples, keratinization and immune function related genes were differentially expressed. In addition, we found that SGs of both diseases may contribute to extracellular matrix remodeling and detected a different set of genes that may be causative for the decreased size and number of SGs in the two diseases. Therefore, SGs are not bystanders in chronic inflammatory skin diseases like PsO and AD, but may actively may modulate inflammation and extracellular matrix remodelling in a disease specific manner.

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A "two-strike" model for psoriasis: an *in vivo* human study

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Imiquimod (IMQ), a TLR 7/8 agonist, was shown to induce a self-limited Th17-dominated contact dermatitis in healthy skin, but not the full picture of psoriasis. Whilst such an innate "first strike" of IMQ is needed for inducing inflammation, a "second strike" might perpetuate inflammation and induce the characteristic phenotype of psoriatic plaques. Here, IMQ was tested on clinically healed plaques of 5 psoriasis patients for inducing a "second strike", namely the activation of $CD103^+$ tissue-resident memory T cells (T_{RM}) that recognize specific cutaneous antigens and thereby maintain the inflammatory response in the skin. Former psoriatic lesion (FL) and never-affected area as control (NL) were treated with IMQ 5% cream, 0.2 g/cm^2, twice a week for 4 weeks. Skin biopsies (n=2) were collected at baseline and day 28 from each site and processed for histology, FACS and bulk RNA-seq analysis. Only 1 patient showed the full clinical and histological picture of psoriasis in activated FL. Results were also confirmed by transcriptome analysis using an existing dataset on psoriasis. Moreover, an increased number of $CD4^+CD103^+KI67^+$ cells was detected in the skin of this patient compared to the others. Interestingly, preliminary data hints at triggering of T cell proliferation by autoantigens from the skin in this patient. We validated for the first time a "two-strike" model for psoriasis, potentially leading to "treat hard and early" concepts to avoid the accumulation of T_{RM} in the skin and thus prevent relapse-remitting affection of the same sites.

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Impaired frequency and function of transitional B cells in patients with pemphigus vulgaris

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Pemphigus vulgaris (PV) is an autoimmune disease clinically characterized by blisters on the skin and/or mucosa. Pathophysiologically, PV is mediated by close interaction of B cells and autoreactive T cells, inducing proliferation, differentiation, and production of autoantibodies targeting desmosomal adhesion proteins, namely desmoglein 3 and/or 1. To elucidate B cell changes at different stages of PV, canonical B cell populations, like naïve, memory, transitional, non-switched, switched B cells, and plasmablasts were monitored in peripheral blood. Our results revealed that transitional B cells, which represent a crucial link between immature B cells in the bone marrow and mature peripheral B cells, were significantly decreased in active PV patients, i.e. newly diagnosed and chronic, compared to remittent PV patients and healthy controls. Moreover, after B cell depletion therapy, their frequencies in active patients recovered to levels of healthy controls, suggesting a deficit in this population may contribute to the PV pathophysiology. As a regulatory role of transitional B cells under inflammatory conditions was suggested in other autoimmune diseases, we determined their regulatory capacity via TGF-β, IL-10, and IL-35 secretion but also pro-inflammatory IL-6. Interestingly, transitional B cells from active patients were refractory to further stimulation by CpG and CD40L, resulting in diminished production of regulatory cytokines. Thus, our findings indicate that both diminished frequency and decreased regulatory capacity of transitional B cells in active stages render them unable to effectively inhibit autoimmune processes in PV.

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Characterization of a murine model of dermatitis induced by oxazolone

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Atopic dermatitis (AD) is a chronic, relapsing, inflammatory skin disease characterized by pruritus and eczematous skin lesions. It has been described that the repeated topical application of the hapten oxazolone to the ears of sensitized mice cause lesions that mimic some features of AD. However, in most of the published reports the number of challenges is significantly high (6 to 12), which translates into a long duration of the assay and causing a significant distress to the animals. In the present study we have characterized a model of dermatitis induced by 4 challenges of oxazolone applied on days 7, 9, 11 and 14 post-sensitization. Ear samples were obtained on day 15. Using this protocol, the main clinical signs consist of an increase in ear skin thickness and erythema. Histological analysis reveals the presence of a diffuse, moderate acanthosis with frequent areas of parakeratosis and pustules. A dermal infiltration of macrophages, lymphocytes and polymorphonuclear cells, as well as proliferation of fibroblasts is also observed. Skin biopsies show increased levels of mRNA expression of 11 cytokines, including the Th2 markers IL-4, IL-13, IL-22 and IL-31, and a reduction in the expression of loricrin, indicating barrier disruption. To further validate the model, we assessed the effect of commercial formulations of the anti-inflammatory drugs betamethasone, tacrolimus and crisaborole. The three topical treatments were able to reduce ear thickness, erythema and the expression of IL-4, IL-13 and IL-33, whilst increasing that of loricrin. Of note, betamethasone inhibited IL-22 expression whereas tacrolimus increased it and crisaborole had no effect at all. Overall, our results show that this model replicates several AD features and respond to approved topical drugs, making it suitable for screening purposes.

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T cells in resolved allergic contact dermatitis drive inflammation and MMP-12–driven tissue modulation

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Pathogenic memory T cells are implicated in the local relapse of allergic contact dermatitis (ACD), vitiligo and psoriasis. Here we investigate how resident T cells initiate relapses in response to the allergen Methylisothiazolinone (MI). MI–related ACD was sampled two months and two years after resolution of disease. T cells were activated in skin explants with MI or the pan T-cell agonist OKT-3. Epidermis was analysed by RNAseq, Nanostring and multiplex methods. Metalloproteinase 12 (MMP-12)–induction by ACD–related cytokines was assessed in primary keratinocytes and fibroblasts and a humanized xenograft mouse model was used. *Ex vivo* activation of T cells in resolved ACD induced chemokines and cytokines involved in immune cell recruitment and tissue remodeling, including the collagenase MMP-12. In response to cytokine stimulation, human primary fibroblasts and keratinocytes had the capacity to overexpress and release MMP-12. Local injections of MMP-12 and ACD–associated cytokines *in vivo* resulted in degradation of the Collagen IV–rich basement membrane separating the epidermis and dermis and a redistribution of T cells within the skin. Resident T cells in resolved ACD induce MMP-12–driven tissue remodeling that facilitates recruitment of local T cells. Our findings emphasize the potential for topical T cell eradication to promote deep remission of relapsing inflammatory dermatoses.